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Neuropsychological Outcomes of COVID-19: A Multicenter, Cross-Cultural Study of Patients Referred for Outpatient Assessment

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Abstract: Objective: Cognitive dysfunction is one of the most frequently reported symptoms in post-acute sequelae of COVID-19 (PASC) and has become a common reason for neuropsychological referral. While data are emerging, we aimed to address possible cross-cultural patterns of neuropsychological outcomes that remain underexplored. Methods: In this cross-sectional, retrospective study, we characterize the cognitive performance, demographic makeup, and clinical characteristics of 84 PASC patients (M_{age} = 57 years) referred for neuropsychological evaluation to three USA sites and one in Germany. Neuropsychological data (mean demographically adjusted z-scores and frequencies of impairment) were examined across six cognitive domains. Independent t-tests compared performances of previously hospitalized and non-hospitalized patients. Results: Patients were assessed on average seven months post-COVID-19 infection. The majority were women and non-hospitalized. Mean cognitive performance was within the normative range, but high variability existed within and between sites. Deficits were generally mild and most frequent in processing speed (range across sites: 9–57% of patients), executive functioning (range across sites: 4–43% of patients) and attention/working memory (range across sites: 0–43% of patients). Hospitalized patients showed greater cognitive impairment than those not requiring hospitalization. Mood symptoms and fatigue/sleep disturbance were more frequent than objective cognitive impairments. At the time of assessment, most patients were unable to return to work. Conclusions: Cognitive performance in clinically referred PASC patients was, overall, within the normative range. Mild deficits were most frequent in time-based attentional/executive tasks. Other factors, such as affective symptoms and fatigue, were frequent and may significantly impact functioning, perhaps more than cognition. Further work with larger samples and longitudinal measures is needed to clarify the impact of COVID-19 on cognitive function and psychiatric distress.

Keywords: SARS-CoV-2; neuropsychological assessment; cognitive dysfunction; cross-cultural; post-acute sequelae of COVID-19

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1. Introduction

Since its initial identification, the impact of coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been far-reaching,

leading to devastating public health burden worldwide. Ongoing efforts to better characterize COVID-19's clinical repercussions have revealed that its clinical manifestations can range from asymptomatic and mildly symptomatic, to acute respiratory distress syndrome (ARDS) and death [1]. While the most prominent symptoms of COVID-19 are respiratory in nature, there is accumulating evidence that the SARS-CoV-2 virus, similar to other human coronaviruses, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV), can produce a gradient of neuropsychiatric sequelae during both acute and post-acute phases of the diseases [2–7]. At this time, studies exploring the specific impact of the SARS-CoV-2 infection on cognition following the acute phase of illness continue to be a burgeoning area of clinical interest as patients recover from the acute phase of illness and move toward rehabilitative management. To date, most studies have examined cross-sectional samples of post-hospitalized patients. Findings have revealed that these patients display the most pronounced deficits in reaction time [8], sustained attention [9,10], and executive functions [11–13]. Several factors have been found to relate to cognitive functioning in patients with COVID-19 following hospital discharge, including length of hospital stay [14], premorbid cognitive functioning [15], and serum C-reactive protein (CRP) levels at the time of admission. Other factors known to be associated with increased risk of developing severe complications, such as pre-existing conditions and medical comorbidities, as well as longstanding systemic health and social inequities that have contributed to a disproportionate burden of COVID-19 among underrepresented racial/ethnic minority groups [16], remain understudied.

It is now well-documented that, for many patients, symptoms may persist into the post-acute phase and beyond [17–19]. This phenomenon is not exclusive to patients who experienced severe COVID-19 symptoms, as similar persistent and debilitating issues have been described in patients who experienced only mild initial COVID-19 illness [8,20]. For example, in a study of non-hospitalized COVID-19 patients with residual neurologic symptoms (i.e., "brain fog," headache, dysgeusia, anosmia, myalgia) five months after acute viral illness, 53% of patients had an abnormal neurological exam and lower than expected performance on cognitive measures of attention and working memory, compared to a demographic-matched U.S. normative population [21]. Nonetheless, less evidence is available from clinical-based settings, and it remains to be seen whether such evidence and observed cognitive profiles translate to other cultural and socioeconomical groups.

Thus, in the current study, we sought to retrospectively characterize cognitive performance in PASC patients with persistent cognitive concerns who were referred for outpatient neuropsychological evaluation. As an international, multi-site collaboration, our aim was also to describe possible cross-cultural contributions to the pattern of neuropsychological outcomes in PASC.

2. Materials and Methods

2.1. Design and Sampling

We report cross-sectional findings of a multi-site, retrospective consecutive sample of adult patients referred for neuropsychological evaluation in the context of cognitive changes after confirmed COVID-19 infection. The sample is non-probabilistic and was selected based on convenience in three clinics in the United States of America (USA, Division of Medical Psychology at the Johns Hopkins Hospital in Baltimore, Maryland (JH DMP), the Massachusetts General Hospital Psychology Assessment Center in Boston, Massachusetts (MGH PAC) and the Massachusetts General Hospital Multicultural Assessment and Research Center in Charlestown, Massachusetts (MGH MARC)) and one clinic in Germany (Department of Neurology of the RWTH Aachen University Hospital in Aachen (UKA)). These sites were selected by a working group of clinical researchers affiliated with the International Neuropsychological Society (INS) Special Interest Group in COVID-19 who had a mutual goal of examining neuropsychological outcomes in a cross-cultural sample of PASC patients.

The JH DMP is a clinic dedicated to clinical neuropsychology and consultation–liaison psychology; patients within the JH DMP subsample were referred from their post-acute COVID-19 team clinic. The MGH PAC is an outpatient clinic dedicated to clinical neuropsychological assessment for patients across the lifespan. The MGH MARC is an outpatient clinic comprised of bilingual (English/Spanish) clinicians dedicated to multicultural neuropsychological assessments for adult patients; patients within the MGH PAC and MGH MARC subsamples were referred primarily from the MGH COVID-19 Survivors Clinic and from MGH specialty (e.g., neurology, psychiatry, etc.) and primary care providers. Patients from the UKA were referred to the Memory or Neurological Post COVID-19 outpatient clinics of the Department of Neurology, either via internal referral (Pneumology or general Neurology outpatient clinics), general practitioner, or an external assisting neurologist.

We emphasize that our investigation is based on retrospective analyses of clinical referrals for outpatient neuropsychological evaluation. No control group was used, and no a priori hypotheses were formulated. Rather, the current study utilized an exploratory approach with normative data used from standardized measures for purposes of comparison. Patients were deemed eligible for inclusion if they had been referred for clinical neuropsychological assessment after COVID-19 illness and did not have a pre-existing diagnosis of dementia or other acquired cognitive disorder. We refer to patients who were hospitalized during the acute phase of COVID-19 infection as 'hospitalized' and those who did not require hospitalization as 'non-hospitalized.'

2.2. Ethical Considerations

The study was approved by the Massachusetts General Brigham Human Research Review Board, the Institutional Review Boards of John Hopkins Medicine, and the Ethics Committee of the RWTH Aachen Faculty of Medicine (EK192/20). Any shared data across sites were de-identified.

2.3. Outcome Variables and Statistical Analyses

We collected data on demographics (sex, age, education, race, and ethnicity) and clinical characteristics (time since infection, need for hospitalization, comorbidities) for all patients. Information on subjective complaints and psychosocial outcomes (e.g., ability to return to work) were captured by self-report. All patients underwent comprehensive neuropsychological evaluations in their primary language (English, Spanish, or German); no tests were translated. Evaluations included standardized measures of cognition and mood (depression and/or anxiety). Test batteries varied slightly across patients, as test selection was individualized based on the clinical referral, setting of assessment (i.e., in-person versus telehealth), and language of test administration (i.e., English, Spanish, or German). Patients' raw scores were compared to normative data—adjusted for age, years of formal education, and/or other variables depending on availability and appropriateness (e.g., primary language, sex, type of electronic device, country of origin, etc.)—and standardized z-scores were calculated. The same normative data used for in-person testing was applied when telehealth assessments were conducted, as prior studies show a very high level of concordance in patients' performances between both testing modalities [22]. Composite z-scores were created for the following six cognitive domains: language/semantic access, processing speed, executive functioning, attention/working memory, memory encoding, and delayed memory. These cognitive domains are common to comprehensive neuropsychological examination and were selected in this study to facilitate examination of differences in performance by domain across sites and between hospitalized and non-hospitalized patients. See Table S1 for a list of site-specific neuropsychological measures by composite. Impairment was defined as composite z-scores $\geq$ 1.5 standard deviations below the mean. Composite z-scores of patients who were hospitalized and non-hospitalized during the acute stages of illness were compared using independent t-tests and effect sizes (Cohen's *d*). Statistical analyses were conducted using IBM SPSS Statistics for Windows,

version 20.0, (IBM Corp., Armonk, NY, USA) with an alpha <0.05 as the statistical threshold for significance.

3. Results

As shown in Table 1, a total of 84 patients were assessed between July 2020 and May 2021, on average 7 months (range 1–13 months) after SARS-CoV-2 infection. The majority were female; age (range 22–85 years). Years of education (range 5–20 years) broadly spanned but differed slightly across sites. Patients from MGH MARC and JH DMP were older and had lower educational attainment. While the majority of our sample self-identified as White or European, race and ethnicity varied by site: UKA (97.6% European; 2.4% North African, Middle Eastern, and Central Asian), MGH PAC (88.9% White; 7.4% Hispanic/Latino; 3.7% Black or African American), JH DMP (62.5% Black or African American; 37.5% White), MGH MARC (100% Hispanic/Latino). Approximately half of the patients were assessed via telehealth (virtual administration of tests), with half of the sites conducting only in-person assessment and the remaining sites performing both in-person and telehealth assessments.

The proportion of hospitalized patients ranged from 30% to 100% across sites, with mean hospitalization duration between 14 and 27 days. Within hospitalized patients, the proportion of those needing mechanical ventilation ranged from 15% to 71% across sites. At the time of their hospitalizations, most patients across sites presented with premorbid medical, psychiatric, and/or neurological comorbidities prior to infection. In addition to post-COVID-19 cognitive complaints, the majority of patients also presented with other post-COVID-19 subjective complaints including fatigue (range: 50–81%), sleep difficulties (range: 44–100%), and mood disturbances (range: 19–100%). The frequency of other subjective complaints varied across sites.

At the time of neuropsychological assessment, a significant proportion of patients were unable to return to work at their baseline capacity (range: 48–85%), with the proportion losing employment or requiring PASC-associated disability leave ranging from 0% to 71% across sites. Between 26% and 50% of patients had or were still receiving physical therapy for post-COVID-19 symptoms. Cognitive interventions were less frequent (0% to 29%) at the time of assessment, but such interventions were frequently recommended, based on cognitive performance.

The proportion of PASC patients exhibiting at least mild impairment (z-scores ≤ -1.5) in at least one cognitive domain varied across sites (range: 0–57%), with patients from MGH MARC showing the highest rates of impairment, and those from UKA showing the lowest. When a more liberal impairment cutoff z-score of >1 standard deviation below the mean was applied, the proportion of patients exhibiting impairment in at least one cognitive domain increased (range: 0–86%), with similar trends in impairment distribution by site (MGH MARC: highest; UKA: lowest) (see Table 2).

Mean z-scores for each cognitive domain were > -1.5 (above the cutoff for impairment) across sites. However, when the more liberal impairment cutoff z-score was applied, patients within the JH DMP showed cognitive impairment in processing speed, executive functioning, and attention/working memory. Patients within the MGH MARC also showed cognitive impairment in processing speed and executive functioning, as well as in encoding and delayed memory (see Table 2). Importantly, there was significant variability both across and within sites (see Figure 1).

Despite variability and differing impairment cutoff scores, the most robust findings (see Table 2 and Figure 1) across sites were deficits in processing speed, followed by executive functioning and attention/working memory. Although still generally within the normative range, compared to non-hospitalized patients (see Table 3 and Figure 1), hospitalized patients exhibited greater impairment in processing speed and executive functioning, with medium to large effect sizes.

Table 1. Post-COVID patient demographics and clinical characteristics by site.

	Site			
	UKA [a] (*N* = 42)	**MGH PAC [b] (*N* = 27)**	**JH DMP [c] (*N* = 8)**	**MGH MARC [d] (*N* = 7)**
Variable				
Sex (F/M)	24/18	19/8	3/5	3/4
Race/Ethnicity (% White or European)	97.6%	88.9%	37.5%	0%
Age (years)	48.39	51.93	64.3	63.57
Range	22–65	25–84	44–85	51–79
Education (years)	15	16	13	9
Range	9–20	12–20	6–16	5–13
Time from COVID Diagnosis to NP Evaluation (months)	6.58	7.55	4.30	10.57
Range	1–12	2–10	2–7	9–13
Date of COVID Diagnosis	February 2020–January 2021	March 2020–January 2021	April 2020–November 2020	March–April 2020
Conducted Remotely	0%	93%	63%	0%
Date of NP Evaluation	August 2020–April 2021	July 2020–May 2021	July 2020–February 2021	October 2020–April 2021
Language of Test Administration	German	English	English	Spanish
	% Yes			
Comorbidities Prior to COVID				
Medical	62%	96%	88%	100%
Psychiatric	14%	56%	38%	43%
Neurologic	36%	44%	75%	0%
Primary Referral due to COVID	99%	93%	100%	100%
Self-Reported Post-COVID Symptoms				
Brain Fog/Cognitive Changes	71%	100%	100%	100%
Fatigue	55%	81%	50%	71%
Mood Disturbance	19%	67%	63%	100%
Sleep Difficulties	48%	44%	50%	100%
Dysautonomia	24%	15%	0%	43%
Psychosocial Distress	-	26%	38%	100%
New Pain	10%	37%	63%	43%
Hospitalized	38%	30%	100%	71%
Days Hospitalized (mean)	26.93	24.50	24.80	14.00
Received Inpatient Treatment	40%	30%	75%	71%
On Ventilator	46%	15%	40%	71%
Delirium	2%	11%	38%	29%
Loss of Employment	0%	4%	67%	71%
Unable to Return to Work at Baseline Capacity	48%	85%	50%	71%
Financial/Housing Strain	-	18%	25%	57%
Grief/Health Impact on Family Members	2%	4%	0%	57%
Post-COVID Treatment				
Physical Rehabilitation	36%	26%	50%	29%
Cognitive Intervention	14%	4%	0%	29%

Note: NP = neuropsychological. [a] Department of Neurology of the RWTH Aachen University Hospital (UKA), Aachen, Germany. [b] Massachusetts General Hospital, Psychology Assessment Center, Boston, MA, USA. [c] Division of Medical Psychology at Johns Hopkins Hospital, Baltimore, Maryland, US. [d] Massachusetts General Hospital Multicultural Assessment and Research Center, Boston, MA, USA.

Table 2. Cognitive test results by domain and site.

	UKA [a] (*N* = 42)	MGH PAC [b] (*N* = 27)	JH DMP [c] (*N* = 8)	MGH MARC [d] (*N* = 7)	UKA [a] (*N* = 42)	MGH PAC [b] (*N* = 27)	JH DMP [c] (*N* = 8)	MGH MARC [d] (*N* = 7)
Cognitive Domain	**Z-Score: *M* (*SD*)**				**Patients with Z-Score ≤ −1.0/≤ −1.5**			
Language/Semantic Access	−0.27 (0.66)	−0.28 (0.98)	−0.33 (0.81)	−0.81 (0.65)	12%/4%	18%/11%	0%/0%	43%/29%
Processing Speed	−0.42 (0.67)	−0.98 (1.09)	−1.08 (0.71)	−1.45 (0.89)	14%/9%	37%/26%	63%/38%	86%/57%
Executive Functioning	−0.12 (0.76)	−0.25 (1.02)	−1.15 (0.96)	−1.29 (0.86)	12%/4%	18%/15%	63%/38%	57%/43%
Attention/Working Memory	−0.09 (0.76)	−0.37 (0.90)	−1.08 (0.88)	−0.58 (0.74)	12%/0%	29%/7%	50%/38%	29%/43%
Encoding	−0.24 (0.63)	−0.13 (1.10)	−0.86 (0.76)	−1.14 (0.98)	15%/0%	22%/7%	38%/13%	57%/14%
Delayed Memory	−0.27 (0.66)	0.00 (1.01)	−0.74 (0.80)	−1.37 (0.95)	9%/2%	11%/11%	38%/13%	71%/43%

[a] Department of Neurology of the RWTH Aachen University Hospital (UKA), Aachen, Germany. [b] Massachusetts General Hospital, Psychology Assessment Center, Boston, Massachusetts, US. [c] Division of Medical Psychology at Johns Hopkins Hospital, Baltimore, Maryland, US. [d] Massachusetts General Hospital Multicultural Assessment and Research Center, Boston, Massachusetts, US.

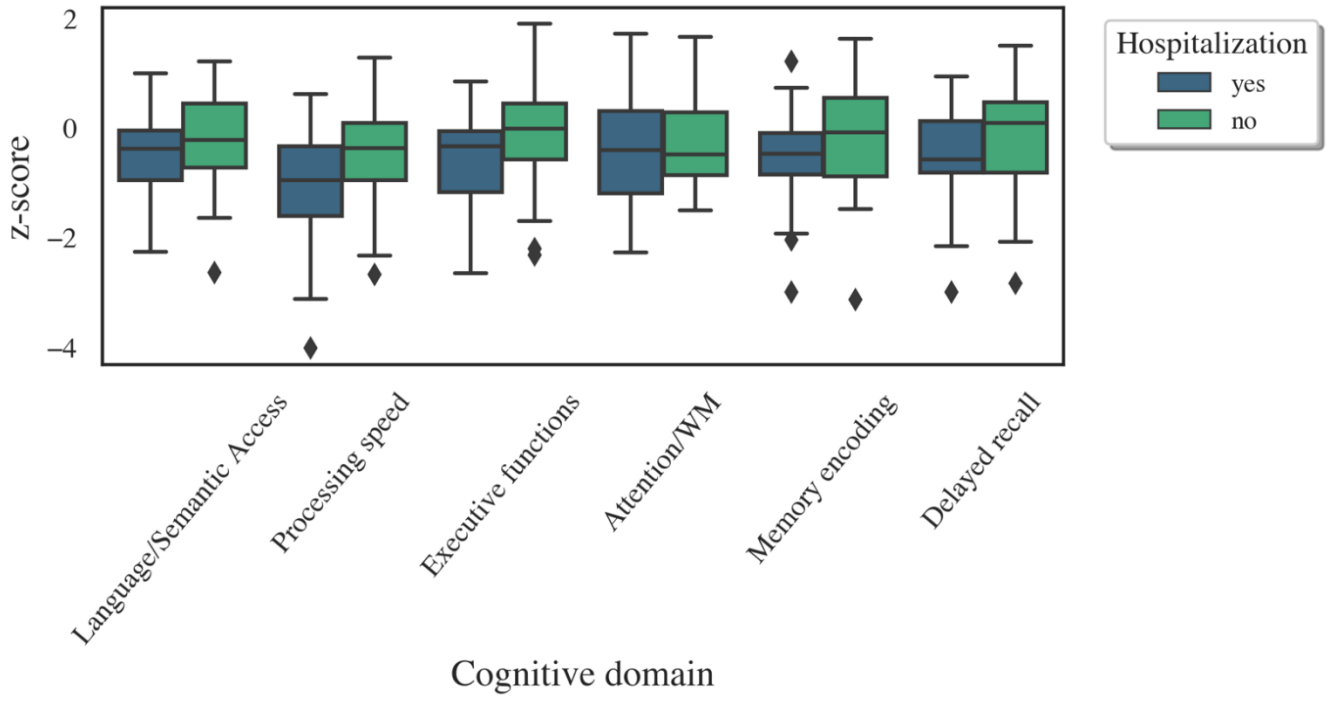

Figure 1. Cognitive performance of PASC patients by cognitive domain and hospitalization status.

Table 3. Group differences in cognitive performance (z-scores) based on hospitalization status during acute COVID-19 illness.

	Hospitalized		Non-Hospitalized				
	n	*M (SD)*	*n*	*M (SD)*	*t (df)*	*p*	*Cohen's d*
Language/Semantic Access	33	−0.48 (0.76)	48	−0.21 (0.79)	1.53 (79)	0.130	0.35
Processing Speed	36	−1.01 (0.97)	48	−0.55 (0.80)	2.35 (82)	0.021 *	0.51
Executive Functioning	36	−0.64 (0.95)	48	−0.15 (0.91)	2.43 (82)	0.017 *	0.53
Attention/Working Memory	33	−0.44 (0.98)	42	−0.27 (0.77)	0.83 (73)	0.408	0.19
Memory Encoding	36	−0.53 (0.86)	47	−0.19 (0.90)	1.76 (81)	0.082	0.39
Delayed Memory	36	−0.49 (0.83)	47	−0.18 (0.93)	1.59 (81)	0.117	0.35

Note. * $p < 0.05$.

Within the MGH PAC (77%), MGH MARC (71%), and JH DMP (67%), most patients reported at least mild depressive symptoms, compared to a smaller percentage within the

UKA (24%). Across sites, over one third to one half reported at least mild anxiety symptoms (MGH PAC: 37%; MGH MARC: not formally assessed; JH DMP: 50%; UKA: 52%).

4. Discussion

To our knowledge, this is one of the first multicenter, international studies of neuropsychological outcomes of COVID-19 in a sample of both hospitalized and non-hospitalized patients who were clinically referred for neuropsychological examination based on persistent cognitive concerns. Accordingly, we are in a unique position to comment on (1) salient similarities across sites, to help inform disease impact on cognition globally and (2) notable differences between sites, to help identify possible sociocultural factors affecting disease outcomes.

Within our sample, the frequency of cognitive impairment varied across sites, with up to 57% of PASC patients exhibiting impaired performance (z-score ≤ -1.5) in at least one of six cognitive domains (up to 86% exhibited impairment when more a more liberal cutoff z-score of ≤ -1 was applied). Among patients who exhibited impairment, the most robust findings were in processing speed, followed by executive functioning and attention/working memory; there was more variability within the findings on memory (encoding and delayed memory) and language/semantic access domains across sites. At the individual test level, patients tended to exhibit the most difficulty on executive tasks that were time-based (e.g., verbal fluency).

Our results are generally consistent with the recent, emerging literature on neuropsychological outcomes after COVID-19, describing deficits in processing speed, basic and sustained attention, working memory, and executive functioning [6–8,10,11,19,21,23,24]. While systematic reviews [6,25] have reported that global cognitive impairment is frequent in PASC patients compared to matched controls, most studies have relied on cognitive screening measures (e.g., MoCA, MMSE), which may not adequately capture PASC cognitive deficits [26]. Overall, our findings suggest that COVID-19 infection may have an impact on fronto–striatal networks, which are known to support cognitive efficiency, attention, and executive processes.

Although most patients presenting with PASC experienced a milder disease severity in the acute phase [27], it is generally assumed that severity of illness, for which we used the need for hospitalization as a proxy, and its associated factors or complications (e.g., delirium, treatment, mechanical ventilation) may be associated with worse cognitive outcomes. As such, patients hospitalized with severe COVID-19 illness may be at an increased risk of neuropsychiatric sequelae [5,28]. Similar to previous reports [6,8,10,11,13,29–32], the cognitive profile of hospitalized patients within our sample was subtle but depressed relative to non-hospitalized patients. From the comparisons between these groups, hospitalized patients showed greater impairment, particularly in processing speed and executive functioning. This is in agreement with previous studies on cognitive outcomes after hospitalization due to COVID-19, that describe marginal rates of impairment in executive and memory functions [29,33], in addition to deficits in attention, processing speed, and memory encoding, with preservation of consolidation [8,13]. On average, our patients were evaluated further out from acute infection than patients described in previous reports. The finding that cognitive impairment was still detected in a similar percentage of patients raises concerns regarding the persistence of cognitive symptoms and the need for post-acute cognitive rehabilitation services.

The question remains whether cognitive impairments, both acute and post-acute, following COVID-19 infection are distinct from those seen in post-infectious syndromes and critical illness more generally. The prevalence of cognitive dysfunction in patients recovering from ARDS alone (approximately 80%) is higher than what we observed in PASC regardless of ARDS [34]. The cognitive pattern we describe, namely subtle deficits in processing speed, executive functioning, and memory beyond the acute illness phase, is nevertheless similar to that which has been described in studies assessing cognitive outcomes following critical illness, and specifically those after ARDS [34–36]. Given the

small sample size, we were not able to address the role of specific treatment modalities, such as mechanical ventilation and oxygenation, or complications, such as delirium, which are known to also impact neuropsychological functioning [37], although this should be addressed in future studies and taken into consideration in clinical practice.

While our study sheds light on the impact of COVID-19 cross-culturally, we acknowledge key differences across sites. First, the MGH MARC (100% Hispanic/Latino population; high percentage of hospitalized patients) and JH DMP (62.5% Black or African American population; only hospitalized patients) had the highest percentage of cognitively impaired patients. This could reflect demographic confounders associated with the older age and lower educational level of both groups, but also a higher severity of illness. Referral bias at these sites, whereby the threshold for referral for neuropsychological evaluation was high, such that only the most severely affected patients were referred or sought out consultation for persistent symptoms, is also a likely contributing factor. Correspondingly, the MGH MARC and JH DMP sub-samples also presented with high percentages of psychosocial burden (e.g., loss of employment/PASC-associated disability) relative to other sites. The high cognitive and psychosocial burden on these sub-samples may reflect longstanding systemic health and socioeconomic inequities, which have been identified as contributors to a disproportionate burden of COVID-19 among traditionally underserved groups [16]. Although these interpretations warrant caution, given the smaller sample sizes of those sites, they undoubtedly justify the need for further evidence regarding the impact of cultural and socioeconomical factors on post-COVID-19 neuropsychological outcomes.

Another notable difference identified across our sites was that a higher percentage of patients (67–77%) within the USA-based sub-samples reported at least mild depressive symptoms than the UKA site (24%). Conversely, patients within the UKA sub-sample reported higher levels of anxiety (52%) than the USA-based subsamples ($\leq$50%). While this may reflect differences in how depression and anxiety are operationalized across different self-report mood questionnaires, we need to consider the possibility that psychological outcomes in COVID-19 may manifest differently based on culture.

Prior literature has shown that COVID-19 infection is associated with high rates of anxiety, depression, fatigue, sleep disruption, and post-traumatic stress (see Vanderlind et al. [25], for a review), which raises the importance of such factors and their impact on patients' cognitive and functional status. Consistent with previous findings, most patients within our sample reported at least mild depressive symptoms and nearly half reported at least mild anxiety symptoms on self-report questionnaires; many patients also reported high levels of fatigue and sleep disturbance.

Overall, the rates of psychiatric symptoms (depression; anxiety) and fatigue/sleep disturbance in our sample were greater than the proportion of patients exhibiting cognitive impairment on objective testing. Given that the vast majority of patients in our sample reported subjective cognitive impairment ("brain fog"), this finding raises the possibility that mood and fatigue may have a greater influence on PASC patients' perception or experience of cognitive functioning, as reported by previous studies [8]. Further, higher rates of post-COVID-19 psychiatric symptoms and fatigue may have a greater impact on patients' quality of life and functional status than actual cognitive impairment [21].

Notably, most patients in our sample were unable to return to work at their baseline level (per self-report) at the time of assessment, and some patients experienced a loss of employment or required PASC-associated disability. These factors are likely compounded by other psychosocial stressors associated with the COVID-19 pandemic, such as increased social isolation and financial hardships. While these results may reflect patient group characteristics and regional differences regarding health and social care systems, they do highlight the need for cognitive rehabilitation and psychotherapeutic intervention to help patients return to their previous level of functioning.

We acknowledge several limitations that are mostly associated with the inherent characteristics of a retrospective, clinical multicenter study. There are inevitable discrepancies between assessment protocols, particularly between instruments used, availability of

norms (based on language of administration, age and/or education, and lack of adjustment for race/ethnicity), and in-person vs. remote assessment. We strived to achieve uniformity between assessment protocols by calculating composite scores for a priori defined cognitive constructs, based on available normative data. In addition to issues related to intra-individual dispersion, the use of normative data might lead to over- and underestimation of deficits, depending on cohort characteristics and the quality of available normative sets. Such effects may be further influenced by the lack of premorbid estimates. Because the majority of our sample had a high educational level, there is also the risk that normatively within-average performance may actually represent a decline in individual cases, relative to their own premorbid function. While the assessment protocols were quite comprehensive and included all major cognitive domains, we may have overlooked measures with higher sensitivity. Similarly, stand-alone performance validity measures were not uniformly administered, which poses another important limitation, particularly considering the frequency of other symptoms, such as mood disorders and fatigue. Another limitation is that we did not capture the frequency of other symptoms and possible confounders, such as rates of exercise intolerance or postural orthostatic tachycardia syndrome (POTS), both of which are commonly seen in PASC and may impact cognition [38].

Given the relative dearth of data on cognitive outcomes of COVID-19, we cannot comprehensively assess the representativeness and generalizability of our results. Referral bias is likely present, as the vast majority of patients had subjective cognitive complaints, which are frequently associated with other contributing factors such as the presence of affective symptoms and psychosocial distress. Other issues, such as the impact of "long-hauler syndrome" in the media, which may influence patients to over-identify with symptoms, should be taken into consideration when investigating the frequency and characteristics of subjective complaints in this population. We also excluded patients with neurodegenerative disorders to avoid it as a confounder, but the impact of COVID-19 in patients with neurodegenerative disease is an important topic for neuropsychological research and clinical practice. Longitudinal studies are needed to investigate possible phenotypes based on patient and illness characteristics, how cognitive profiles change over time, and rehabilitation efficacy. Given its exploratory design and retrospective clinic samples, our study did not include control or patient comparison groups. Thus, our study cannot determine definitively whether prior COVID-19 infection—independently or in interaction with other risk factors—contributed to the cognitive and psychosocial symptoms assessed herein. The lack of control/comparison groups is a problem in much of the post-COVID-19 syndrome literature and should be addressed in future work.

5. Conclusions

Fundamentally, additional data and stronger evidence is needed to develop a more reliable clinical profile that can inform neuropsychological diagnostic and therapeutic practices in PASC patients. Based on our findings, the use of comprehensive neuropsychological testing is warranted within this population, as deficits may not be captured by commonly used screening instruments (i.e., MoCA, MMSE). Along with our findings demonstrating deficits in processing speed, we highlight the importance of including time-based tasks in cognitive assessment of PASC patients, as reduced cognitive efficiency may emerge as a hallmark of PASC and, in fact, is a common subjective complaint of patients at their initial presentation. When patients do exhibit post-COVID cognitive impairment it is generally mild, and other factors, including affective symptoms, sleep disorder and fatigue, all of which are known to impact cognitive performance and functionality, may also play a significant role. Collectively, our cognitive findings, along with contributions of other persistent, self-reported post-COVID-19 factors (e.g., sleep problems/fatigue; mood symptoms), suggest possible dysfunction within fronto–striatal systems in a subset of PASC patients, although future imaging studies are needed to further examine this hypothesis.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/covid2090092/s1, Table S1: List of neuropsychological measures by site.

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